



MS APPEAL BRIEF - PATENTS  
PATENT  
0020-4883P

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of

Before the Board of Appeals

Hideakira YOKOYAMA et al.

Appeal No.:

Appl. No.: 09/890,552

Group: 1614

Filed: August 2, 2001

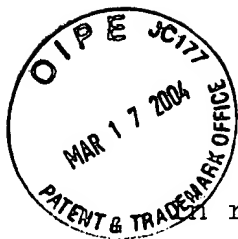
Examiner: D.A. JAGOE

Conf.: 4627

For: DRUG FOR ALLEVIATING MIGRANE

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BRIEF ON BEHALF OF APPELLANTS

MS APPEAL BRIEF - PATENTS  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

March 17, 2004

Sir:

The present Appeal Brief is respectfully submitted in connection with the above-identified application.

(1) REAL PARTIES IN INTEREST

As evidenced by the assignment filed and recorded on August 2, 2001 at Reel # 012067 and Frame # 0231, the Real Parties in Interest are TEIKOKU SEIYAKU CO., LTD. of 567, Sanbonmatsu, Ochi-cho, Ohkawa-gun, Kagawa-ken, Japan and ROHTO PHARMACEUTICAL CO., LTD. of 8-1 Tatsuminishi 1-chome, Ikuno-ku, Osaka-shi, Osaka-fu, Japan.

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**(2) RELATED APPEALS AND INTERFERENCES**

There are no related appeals or interferences.

**(3) STATUS OF THE CLAIMS**

Claims 11, 12, 13, 17, 19, 20 and 21 are pending in the application and stand rejected per the Final Office Action of June 18, 2003.

**(4) STATUS OF THE AMENDMENTS**

The response to the Office Action filed on November 18, 2003 cancelled claims 1-8 and 14-18, amended claim 12 and added new claims 20 and 21. All amendments have been entered as indicated in the Advisory Action dated January 23, 2004.

**(5) SUMMARY OF THE INVENTION**

The present invention is directed to a method of alleviating migraine comprising the steps of administering an effective amount of a drug composition, which consists essentially of as active ingredients l-menthol and one or more essential oils. The essential oils are lavender oil, juniper oil, peppermint oil, rose oil and rosemary oil. The active ingredients are in a pharmaceutically acceptable base to make up the drug composition. The drug composition

is dermally administered to a patient suffering from migraine.

**(6) ISSUES FOR CONSIDERATION**

- A.) Whether the Examiner has made a prima facie showing of obviousness under 35 USC 103(a) for claims 11, 12, 13, 19, 20 and 21 when the Examiner has not established that there is clear motivation to combine the references cited.
- B.) Whether one of ordinary skill in the art can take the disclosure of Gobel et al. Phytomedicine, vol. 2 no. 2 pp. 93-102 (1995) (hereinafter "Gobel") in combination with Davis et al. U.S. Patent 5,665,378 A (hereinafter "Davis '378") and arrive at the present invention of claims 11, 12, 13, 19, 20 and 21.
- C.) Whether the Examiner has made a prima facie showing of obviousness under 35 USC 103(a) for claim 17 when neither Gobel nor Davis '378 disclose or suggest the specific amounts of l-menthol and essential oils in the composition of the present invention of claim 17.

**(7) GROUPING OF THE CLAIMS**

Group 1: Claims 11, 12, 13, 19, 20 and 21; and

Group 2: Claim 17.

(8) ARGUMENTS ON THE ISSUES FOR GROUP 1

A. No Prima Facie Case of Obviousness For Lack of  
Motivation to Combine Gobel et al. with Davis et al.

The Examiner has failed to establish a prima facie case of obviousness by failing to point to motivation or a suggestion to combine the cited references to arrive at all the limitations of the present invention as defined by the broadest claim, claim 11.

According to In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988), a prima facie case of obviousness is established when the Examiner shows that some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the cited references. The Examiner has failed to make such a showing.

The Examiner in an attempt to state a prima facie case asserts in Paper 18, page 9, six lines from the bottom that, "It would have been made obvious to one of ordinary skill in the art at the time it was made to employ l-menthol and an essential oil such as peppermint oil to relieve a migraine headache since peppermint oil is known to impart a cool feel, inhibit substance P and has a muscle relaxing effect and since menthol is known in the pharmaceutical art to promote percutaneous transfer (of the peppermint oil) and menthol has an analgesic and local anesthetic effect in itself."

The Examiner cites Gobel et al. as teaching that essential oils, especially peppermint oil, alleviate headache with local application by generating a longlasting cooling effect on the skin, which is caused by steric alteration of the calcium channels of the cold-receptors. The Examiner also stated that it is known that peppermint oil induces a significant increase of skin blood flow after application. The Examiner concedes that Gobel et al. fails to teach menthol as an analgesic. At best, the Examiner states that Gobel et al. discloses the combination of peppermint oil and ethanol.

The Examiner relies on Davis et al. the secondary reference to compensate for Gobel's failure to disclose l-menthol. The Examiner states that Davis teaches menthol, a secondary alcohol, as an analgesic and as useful to "enhance the percutaneous transfer of systemically active drugs in mammals."

Appellants submit that it is not prima facie obvious to modify a reference unless the references suggest an advantage to be gained from the modification. See In re Sernaker, 217 USPQ 1, 6 (Fed. Cir. 1983). Moreover, the cited references must suggest the desirability of the modification. In re Brouwer, 37 USPQ2d 1663, 1666 (Fed. Cir. 1995). The cited references do not suggest any advantage to be gained by making the Examiner's proposed combination.

Gobel never discloses or suggests the combination of peppermint oil and l-menthol as active ingredients in treating



headache, much less migraine. Gobel fails to suggest an advantage to be gained by combining the teaching in Gobel with that of Davis, since Gobel already teaches effective transdermal administration and the l-menthol in Davis is used as a permeation enhancer. Also, Davis fails to suggest using an essential oil with l-menthol to treat migraine. Davis fails to teach using an essential oil as a systematic drug in the drug delivery system. The Examiner has not pointed to any general knowledge in the art that would motivate one of ordinary skill in the art to combine the two components for the treatment of migraine. The Examiner merely relies on the known physical properties of the components for reason to combine the components. However, this is not the standard for finding obviousness from a combination of disclosures. There must be some specific teaching that there is some advantage to be gained by making the combination. The Examiner has not pointed to any such teaching.

Moreover, the formulation in Davis uses other essential ingredients in alleviating pain. For example, capsaicin is an essential ingredient in the Davis formulation. See column 5, lines 34 to 62. Capsaicin, along with an anti-inflammant and pamabrom are the active ingredients in the formulation in Davis. On the other hand, in Gobel, the essential component of interest is the peppermint oil. Gobel does not suggest adding an additional therapeutic agent to the composition, such as

capsaicin, an anti-inflammatant or pamabrom. Gobel's only suggestion is for further testing of peppermint oil. See page 101, left column, last paragraph. As such, Appellants submit that there is no suggestion or motivation to combine the teachings in Davis with that of Gobel.

As such, Appellants submit that no prima facie case of obviousness has been established. Thus, Appellants respectfully request that the rejection be reversed on this basis alone.

B. The Claimed Invention is Not Obvious In View of the Teachings of Gobel et al. in combination with Davis et al.

The Examiner contends that the present invention is obvious because Gobel teaches peppermint oil for alleviating headache and Davis teaches menthol in a transdermal drug delivery system. Appellants submit that even if one of ordinary skill in the art were motivated to combine the teachings in Gobel and Davis, the teachings still lack sufficient disclosure for one of ordinary skill in the art to successfully obtain the present invention.

The Examiner states that Gobel discloses peppermint oil in combination with ethanol, where the combination is locally applied. Gobel does not appear to explain any significance in combining the peppermint oil with ethanol. Gobel states that the ethanol produced significant sensitization to thermal pain stimuli, however, the sensitization was counteracted by the oil

preparations tested. The Examiner also fails to provide any explanation of the significance of this combination.

Appellants submit that Gobel is concerned with alleviating headache with peppermint oil. Gobel discloses in Table 1, four preparations that were studied on healthy males. The results are shown in Table 5. The preparations contained as follows: Prep 1 → peppermint oil, eucalyptus oil and ethanol; Prep 2 → peppermint oil and ethanol; Prep 3 → eucalyptus oil and ethanol; and Prep 4 → ethanol. The study revealed that Prep 1, which contained peppermint oil, eucalyptus oil and ethanol increases cognitive performance while also having a muscle relaxing and mentally relaxing effect. This preparation had little influence on pain sensitivity. In Prep 2, which contained peppermint oil and ethanol, a significant analgesic effect with a reduction in sensitivity to headache was observed.

Gobel concludes from the study that peppermint oil preparations have significant effects on mechanisms associated with the pathophysiology of clinical headache syndromes.

Note that Gobel neither addresses nor answers the question of whether essential oil preparations are clinically effective in headaches aside from the described experimental laboratory mechanisms. This is noted at page 101, left column, line 7 to the last line from the bottom, which states that a double blind, placebo controlled, randomized study to compare the efficacy of the widely used analgesic paracetamol with different peppermint

and eucalyptus oil preparations should be studied. (See also the Summary (last three lines) at page 93.)

Moreover, Gobel is only associated with headache. Gobel never discloses or suggests that peppermint oil is effective in alleviating migraine. Headache and migraine are very different maladies. See Goodman & Gilman, 9<sup>th</sup> edition (cited by the Examiner), p. 499, last paragraph of the right column, which states that headache pain is unrelated to migraine.

The secondary reference Davis discloses menthol and other components (active drugs) in a drug delivery system. In Davis, menthol is not an active ingredient, but is instead used to enhance the dermal transfer of systemically active drugs.

Applicants submit that an essential oil is not a systemically active drug. Furthermore, eucalyptus oil is disclosed in Davis as a transdermal delivery enhancer and not as an active ingredient. Therefore, if one were to use the teachings in Davis, one would assume that the essential oil is merely a transdermal delivery enhancer and not the active drug.

However, according to Gobel's study report, eucalyptus (Prep 3) was not effective in relieving headache in the tested parameters, and furthermore, Prep 1 was not superior to Prep 2 even in the reduction in sensitivity to headache in spite of the fact that Prep 1 contains eucalyptus either as an active drug or as a permeation enhancer.

As shown in Table 3 of the present specification, the comparative examples, which contain only l-menthol as an active ingredient or peppermint oil as an active ingredient are far inferior in alleviating migraine as compared to both ingredients being synergistically effective in alleviating migraine. Please see the comparative data using volunteers, i.e. patients suffering from migraine, where the present invention, Examples 1, 3 and 5, are compared to Comparative examples 1 and 2. This synergistic effect is not disclosed or suggested in either of the cited references.

At best, the Examiner has pointed out a combination of references that make it "obvious to try" to attain the claimed invention. "Obvious to try" is not the standard under which to reject claims under 35 USC 103. See In re Dow Chemical Co., 5 USPQ2d 1521, 1532 (Fed. Cir. 1988) (rejecting the "obvious to try" standard).

Appellants have successfully demonstrated that one of ordinary skill in the art could not arrive at the present invention from the combination of references cited by the Examiner. As such, Appellants submit that the present invention is not rendered obvious by the combination of Gobel et al and Davis et al.

(9) ARGUMENTS ON THE ISSUE FOR GROUP 2

Appellants submit that claim 17, directed to a method for alleviating migraine comprising the step of administering to a patient in need thereof an effective amount of a drug composition consisting essentially of as active ingredients l-menthol in an amount of 0.01-1% per total weight of the pharmaceutically acceptable base and one or more essential oils selected from the group consisting of lavender oil, juniper oil, peppermint oil, rose oil and rosemary oil in an amount of 0.001-1% per total weight of the pharmaceutically acceptable base.

Gobel discloses peppermint oil in treating headache. In the composition used for treating headache, 10 grams of peppermint oil is used. From the examples in preparations 1 and 2, it is determined that the peppermint oil makes up at least 10 weight % of the composition in Gobel. See where 10 grams of peppermint oil is used with a trace amount of eucalyptus oil and 90% ethanol to 100 grams total weight for preparations 1 and 2.

Davis discloses menthol as a permeation enhancer in a transdermal therapeutic formulation. In the formulation in Davis, menthol makes up at least 15 % of the total weight of the formulation. See column 6, line 28-35 and claim 5 of Davis.

Gobel fails to disclose or suggest peppermint oil in an amount within the range of the essential oils of claim 17. Likewise, Davis fails to disclose or suggest l-menthol in an amount within the range of l-menthol of claim 17.

As such, Appellants submit that the subject matter of claim 17 is free of any rejection based on the combination of Davis and Gobel. Therefore, the rejection of claim 17 should be reversed as no prima facie case of obviousness has been established.

**(10) Conclusion**

For the foregoing reasons, Appellants respectfully request that the rejection be reversed and that the claims be permitted to pass to allowance.

The required Appeal Brief fee in the amount of \$330.00 is attached hereto.

If necessary, the Commissioner is authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or 1.17, particularly, extension of time fees.

Respectfully submitted,

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CLAIMS APPENDIX

Claims 1-10. (Canceled)

Claim 11. (Previously Presented) A method for alleviating migraine comprising the step of:

administering to a patient in need thereof an effective amount of a drug composition consisting essentially of as active ingredients 1-menthol and one or more essential oils selected from the group consisting of lavender oil, juniper oil, peppermint oil, rose oil and rosemary oil in a pharmaceutically acceptable base; and

wherein said drug composition is dermally administered.

Claim 12. (Previously Presented) The method claimed in claim 11, wherein the drug composition is in the form of a patch or an ointment.

Claim 13. (Previously Presented) The method claimed in claim 11, wherein an application region of the drug composition is face, forehead, nape of the neck or temple.

Claims 14-16. (Canceled)



Claim 17. (Previously Presented) The method claimed in claim 11, wherein the amounts of l-menthol and one or more essential oils are 0.01-1% by weight per total weight of the pharmaceutically acceptable base and 0.001-1% by weight per total weight of the pharmaceutically acceptable base, respectively.

Claim 18. (Canceled)

Claim 19. (Previously Presented) A method for alleviating migraine comprising the step of:

administering to a patient in need thereof an effective amount of a drug composition consisting essentially of as active ingredients l-menthol and one or more essential oils selected from the group consisting of lavender oil, peppermint oil and rose oil in a pharmaceutically acceptable base; and

wherein said drug composition is dermally administered.

Claim 20. (Previously Presented) A method for alleviating migraine comprising the step of:

administering to a patient in need thereof an effective amount of a drug composition consisting essentially of synergistically as active ingredients l-menthol and one or more essential oils selected from the group consisting of lavender

oil, peppermint oil and rose oil in a pharmaceutically acceptable base; and

wherein said drug composition is dermally administered.

Claim 21. (Previously Presented) A method for alleviating migraine comprising the step of:

administering to a patient in need thereof an effective amount of a drug composition consisting essentially of as synergistically active ingredients l-menthol and one or more essential oils selected from the group consisting of lavender oil, juniper oil, peppermint oil, rose oil and rosemary oil in a pharmaceutically acceptable base; and

wherein said drug composition is dermally administered.